BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

PATENT SPECIFICATION

NO DRAWINGS

Inventors: JOHN WILLIAM JAMES and RONALD ERNEST RODWAY

1,135,947

1,135,947

Date of filing Complete Specification: 19 April, 1966.

Application Date: 20 April, 1965. No. 16662/65.

Complete Specification Published: 11 Dec., 1968.

Index at acceptance: —C2 C(1F2C6, 1F2D3, 3A14A3A, 3A14A5, 3A14A8D, LK29X, LK29Y, LK32Y, LK213, LK220, LK226, LK250, LK251, LK322, LK323, LK351, LK352, LK650, LK761, LK762, LP29X, LP29Y, LP32Y, LP213, LP250, LP251, LP323, LP332, LP621, LP650, LP671, LP681)

Int. Cl.: —C 07 d 39/02

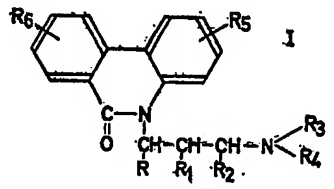
COMPLETE SPECIFICATION

Novel Biologically Active Derivatives of Phenanthridone

We, ASPRO-NICHOLAS LIMITED, a British company, of 16 Berkeley Street, London W.1., England, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

This invention relates to novel biologically active derivatives of phenanthridone, to pharmaceutical compositions containing such derivatives and to a method of treatment involving the administration of said derivatives and compositions. This invention is further concerned with processes for manufacturing said novel phenanthridone derivatives.

The phenanthridone derivatives (i.e. derivatives of 5,6 - dihydro - 6 - oxophenanthridine) of the present invention are of the general formula: —



I

wherein R, R_1 and R_2 each represent a hydrogen atom or methyl radical; R_3 and R_4 each represent a hydrogen atom; a lower alkyl radical; a cycloalkyl radical or an aralkyl radical; or together with the adjacent nitrogen atom R_3 and R_4 form a heterocyclic ring, which ring may contain a further hetero atom such as an oxygen or nitrogen atom (which further nitrogen atom may be substituted by a lower alkyl or hydroxyalkyl radical); and R_5 and R_6 each represent a hydrogen or halogen atom or a lower alkyl, alkoxy, alkylthio, trifluoromethyl, nitro, amino, hydroxyl, cyano or sulphamoyl radical. By the term "lower alkyl" as used herein we mean to include saturated and unsaturated alkyl radicals containing up to four carbon atoms and preferably 1 to 2 carbon atoms. Such phenanthridone derivatives may be used for the purposes of this invention either as such or more preferably as suitable non-toxic pharmaceutically acceptable acid addition salts.

The present invention is particularly concerned with compounds of formula I in which R, R_1 and R_2 are as specified above; R_3 and R_4 each represent a hydrogen atom, a lower alkyl or aralkyl radical or, together with the nitrogen atom, R_3 and R_4 represent a heterocyclic ring which may contain a further nitrogen or an oxygen atom; R_5 is as previously specified and R_6 is a hydrogen or halogen atom or a lower alkyl or trifluoromethyl radical.

This invention is most particularly concerned with compounds of formula I in which R_5, R_1, R_2 and R_6 are hydrogen atoms; R_3 and R_4 each represent a hydrogen atom or a lower alkyl or aralkyl radical or, together with the nitrogen atom, R_3 and R_4 form a heterocyclic ring which may contain a further nitrogen or an oxygen atom, and R_5 is a hydrogen or halogen atom or a lower alkyl, nitro, amino or hydroxyl radical.

Where R_3 and R_4 form, together with the adjacent nitrogen atom, a heterocyclic ring,

that ring preferably contains from 5 to 7 ring atoms.

It has been found in accordance with the present invention that compounds of formula I possess useful biological properties in that such compounds act through the central nervous system as anti-depressants. Compounds acting in such a way may have very valuable therapeutic uses as potential psychotropic drugs and, accordingly, this invention also provides a method of treatment wherein a dose of one of the active compounds effective for the particular purpose is administered.

The compound in which R, R_1, R_2, R_3 and R_6 are hydrogen atoms and R_5 and R_4 are methyl radicals has been found to have a pharmacological profile showing similarities both to certain substances which depress the central nervous system and to certain substances which stimulate the central nervous system. The compound is therefore to be expected to be particularly useful as a mood elevator.

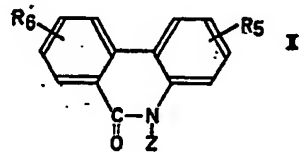
The present invention further provides pharmaceutical compositions comprising as an essential ingredient at least one active compound of formula in association with at least one pharmaceutically acceptable carrier therefor.

The compounds or compositions of the present invention are preferably administered orally, rectally or parenterally in the form of, for example, tablets, capsules, suppositories, suspensions or solutions. Advantageously for this purpose, formulations may be provided in dosage unit form in which each dosage unit preferably contains from 0.5 to 500 mg., more advantageously between 2 and 110 mg., and most advantageously between 4 and 80 mg. of the active ingredient. The term "dosage unit" is used herein as meaning a physically discrete unit containing an individual quantity of the active ingredient in admixture with a pharmaceutical diluent therefor or otherwise in association with a pharmaceutical carrier; the quantity of the active ingredient being such that one or more units are normally required for a single therapeutic administration or that, in the case of severable units such as scored tablets, at least one fraction such as a half or a quarter of a severable unit is required for a single therapeutic administration.

The compositions of the present invention will normally consist of at least one compound of formula I mixed with a carrier, or diluted by a carrier, or enclosed or encapsulated by a carrier in the form of a capsule, sachet, catchet, paper or other container. A carrier which serves as a vehicle excipient or diluent for the active therapeutic ingredient may be a solid, semi-solid or liquid material.

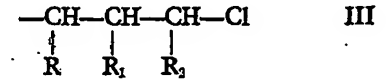
Some examples of the carriers which may be employed in the pharmaceutical compositions of the invention are lactose, dextrose, sucrose, sorbitol, mannitol, starch, gum acacia, calcium phosphate, liquid paraffin, cocoa butter, oil of theobroma, alginates, tragacanth, gelatin, syrup B.P., methyl cellulose, sodium lauryl sulphate, polyoxyethylene sorbitan monolaurate, and methyl and propyl hydroxybenzoates.

According to a further feature of the present invention, there is provided a process for preparing the novel derivatives of phenanthridone represented by the general formula I, which method comprises reacting a phenanthridone of the formula:—



I

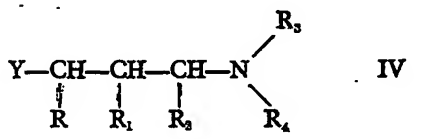
wherein R_5 and R_6 are as defined in formula I and Z is hydrogen or a group of the formula:—



III

wherein R, R_1 and R_2 are as defined in formula I with

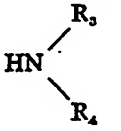
(a) when Z is hydrogen, a compound of the formula:—



IV

wherein R, R_1, R_2, R_3 and R_4 are as defined in formula I and Y is a Cl, Br or I atom or an alkyl- or aryl-sulphonyloxy radical, the reaction being carried out in the presence of a suitable condensing agent, for example, sodium hydride, sodium hydroxide, sodamide or phenyl lithium, preferably in the presence of a solvent or mixture of solvents, for example dimethylformamide, benzene or toluene; and

(b) when Z is a group of formula III, an amine of the formula:—



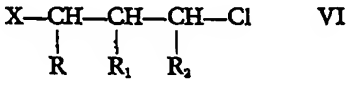
V

wherein R_3 and R_4 are as defined in formula I, the reaction normally being carried out at elevated temperature;

and thereafter, where a compound of formula I in which R_3 and/or R_4 is a hydrogen atom

is required and it not obtained by the foregoing method, reducing the corresponding compound of formula I in which R_3 and/or R_4 is an aryl methyl radical, for example a benzyl or 2-furfuryl radical, using, for example, hydrogen in the presence of a hydrogenation catalyst, for example palladium on charcoal.

The compounds of formula II in which Z is a group of formula III may be prepared by known methods, for example by reacting a compound of formula II in which Z is hydrogen with a compound of the formula:—



VI

wherein X is halogen other than chlorine, for example bromine, or an alkyl- or aryl-sulphonyloxy radical for example a methyl-, benzene or p-toluene-sulphonyloxy radical, the reaction being carried out in the manner described at (a) above.

Salts of the compounds of this invention are particularly acid addition salts, such as the pharmaceutically acceptable non-toxic addition salts with suitable acids, such as those with inorganic acids, for example hydrochloric, hydrobromic, nitric, sulphuric or phosphoric acids, or with organic acids, such as organic carboxylic acids, for example acetic, glycollic, maleic, hydroxymaleic, malic, tartaric, citric, salicylic, *o*-acetyloxybenzoic, nicotinic or isonicotinic acid, or organic sulphonic acids, for example methane sulphonic, ethane sulphonic, 2 - hydroxyethane sulphonic, *p*-toluene sulphonic or naphthalene 2-sulphonic acid. Apart from pharmaceutically acceptable acid addition salts, other salts are also included within the scope of acid addition salts; they may serve as intermediates in the purification of the compounds or in the preparation of other, for example pharmaceutically acceptable, acid addition salts, or are useful for identification, characterization or purification of the bases.

A resulting acid addition salt may be converted into the free compound according to known methods, for example, by treating it with a base, preferably in the presence of water, such as with a metal hydroxide, for example an alkali metal or alkaline earth metal hydroxide, for example lithium hydroxide, sodium hydroxide, potassium hydroxide or calcium hydroxide, a metal carbonate, such as an alkali metal or an alkaline earth metal carbonate or hydrogen carbonate, for example sodium, potassium or calcium carbonate or hydrogen carbonate, ammonia, or with a hydroxyl ion exchange preparation, or with any other suitable reagent.

A resulting acid addition salt may also be converted into another acid addition salt according to known methods; for example, a salt with an inorganic acid may be treated with a metal salt, for example sodium, barium or silver salt, of an acid in a suitable diluent, in which a resulting inorganic salt is insoluble and is thus removed from the reaction medium. An acid addition salt may also be converted into another acid addition salt by treatment with an anion exchange preparation.

A free compound may be converted into an acid adidtion salt according to known methods, for example, by reacting the base, preferably a solution thereof in a solvent or solvent mixture, with the appropriate acid or a solution thereof, or with an anion exchange preparation and isolating the desired salt, which may be obtained in the form of a hydrate or may contain solvent of crystallization.

The following Examples further illustrate the invention:—

Example 1

5 - (3′ - Dimethylaminopropyl) - phenanthridone hydrochloride monohydrate

40 g. (ca 0.2 mole) of phenanthridone was added in portions to sodium hydride (9.5 g. of a 50% dispersion in oil: ca. 0.2 mole) suspended in a mixture of 160 ml. dimethylformamide and 40 ml. benzene. On completion of the addition, the resultant mixture was heated on a steam bath for 1 hour. 24.2 g. (ca. 0.2 mole) of freshly prepared dimethylaminopropyl chloride was then added and the mixture was heated on a steam bath for about 5 hours before being cooled and filtered. The filtrate was concentrated and poured into excess water, the crude base formed being isolated by ether extraction, followed by back extraction with dilute hydrochloric acid (ca. 2.5 *N*) basification, re-extraction with ether and finally removal of the solvent. The crude hydrochloride, obtained by treating an ethereal solution of this product with ethereal hydrogen chloride, was dissolved in water and the basification, extraction and salt formation procedure repeated. Recrystallisation of the crude salt from an absolute alcohol/ether mixture gave 5 - (3′ - dimethylaminopropyl) - phenanthridone hydrochloric monohydrate, m.p. 225—226° C. Analysis of this compound yielded the following results:—

		C(%)	H(%)	Cl(%)	N(%)
	Found	64.6	6.8	10.5	8.55
$C_{18}H_{21}ClN_2O.H_2O$	Requires	64.6	6.93	10.6	8.37

EXAMPLE 2

5 - (3′ - Dimethylaminopropyl) - phenanthridone

An aqueous solution of the hydrochloride salt from Example 1 was basified with dilute aqueous sodium hydroxide and extracted with ether. The crude base obtained by evaporation of the ether was recrystallised from light petroleum (b.p. 40—60° C.) to yield 5 - (3′ - dimethylaminopropyl) - phenanthridone, m.p. 83—84.5° C. Analysis of this compound yielded the following results:—

		C(%)	H(%)	N(%)
	Found	77.1	7.22	9.95
$C_{18}H_{20}N_2O$	Requires	77.2	7.17	9.99

EXAMPLE 3

5 - (3′ - N - Benzyl - N - methylaminopropyl) - phenanthridone hydrochloride

19.5 g. (0.1 mole) of phenanthridone was added in portions to sodium hydride (4.8 g. of a dispersion in oil; 0.1 mole) suspended in a mixture of 100 ml. of dimethylformamide and 10 ml. benzene and after completion of the addition, the solution was heated for 1 hour on a steam bath. 19.8 g. (0.1 mole) of N - benzyl - N - methyl - 3 - chloropropylamine was added to the solution and this mixture heated on a steam bath for 21 hours before being cooled and filtered. The filtrate was concentrated under reduced pressure and poured into excess water. The crude base was isolated by ether extraction, followed by back extraction with dilute hydrochloric acid (ca. 2.5 *N*), basification using sodium hydrogen carbonate and finally re-extraction with ether. After removal of the solvent, the residual oil was re-dissolved in dry ether and the crude salt precipitated by the addition of ethereal hydrogen chloride. On recrystallisation first from methyl ethyl ketone and then from absolute alcohol/ether, 5 - (3′ - N - benzyl - N - methylaminopropyl) - phenanthridone hydrochloride, m.p. 211—213° C., was obtained. Analysis of this compound yielded the following results:—

		C(%)	H(%)	Cl(%)	N(%)
	Found	73.0	6.57	9.18	6.48
$C_{24}H_{25}N_2ClO$	Requires	73.4	6.41	9.02	7.13

EXAMPLE 4

5 - (3′ - Methylaminopropyl) - phenanthridone hydrochloride

A solution containing 8.8 g. (0.02 mole) of 5 - (3′ - N - benzyl - N - methylaminopropyl) - phenanthridone hydrochloride in a mixture of 100 ml. absolute methanol and 150 ml. absolute ethanol was hydrogenated at 1 atmosphere pressure using 0.2 g. of palladium /charcoal as catalyst. Slight warming was required to initiate the reaction. On completion of the hydrogenation, the solution was filtered and then evaporated to dryness under reduced pressure. The crude product obtained was granulated under an ether/acetone solution and finally recrystallised twice from absolute ethanol/ether to yield 5 - (3′ - methylaminopropyl) - phenanthridone hydrochloride m.p. 238—240° C. Analysis of this compound gave the following results:—

		C(%)	H(%)	Cl(%)	N(%)
	Found	67.3	6.40	11.9	8.60
$C_{17}H_{19}N_2ClO$	Requires	67.4	6.32	11.7	9.25

EXAMPLE 5

5 - [3′ - (4″ - Methyl - 1″ - piperazinyl)-propyl] - phenanthridone dimaleate

15.5 g. (ca. 0.08 mole) of phenanthridone was added in portions to sodium hydride (3.8 g. of a 50% dispersion in oil; ca. 0.08 mole) suspended in a mixture of 100 ml. dry dimethylformamide and 10 ml. dry benzene. The mixture was thoroughly stirred during the addition and then heated on a steam bath for about 30 minutes. 17 g. (ca. 0.1 mole) of 1 - (3′ - chloropropyl) - 4 - methyl - piperazine was added with stirring to the above solution and the resultant mixture heated for about 10 hours on a steam bath. After cooling, the product obtained was filtered, the filtrate concentrated to small volume and poured into excess water. The crude base was isolated by ether extraction, followed by back extraction with dilute hydrochloric acid (ca. 2.5*N*), basification, re-extraction with ether and finally removal of the solvent to yield the crude base as an oil.

7.7 g. (ca. 0.023 mole) of this crude base dissolved in 40 ml. tetrahydrofuran was added to 5.4 g. (0.046 mole) maleic acid in 100 ml. tetrahydrofuran and the mixture allowed to stand for about 16 hours at room temperature (20—23° C). The crude salt which precipitated was filtered off and recrystallised from nitromethane to yield 5 - [3′ - (4″ - methyl - 1″ - piperazinyl)propyl] - phenathridone dimaleate m.p. 185—188° C (decomp.). Analysis of this product gave the following results:—

		C(%)	H(%)	N(%)
	Found	61.2	5.88	7.19
$C_{21}H_{25}N_3O.2(C_4H_4O_4)$	Requires	61.4	5.86	7.4

EXAMPLE 6

5 - (3′ - Dimethylaminopropyl) - 3 - chlorophenanthridone hydrochloride hydrate

To sodium hydride (1.4 g. of a 50% dispersion in oil; ca. 0.029 mole) suspended in a mixture of 75 ml. dry dimethylformamide and 15 ml. dry benzene, was added, with stirring, 6.2 g. (0.027 mole) of 3 - chlorophenanthridone and the mixture heated for a half hour on a steam bath. 3.6 g. (ca. 0.03 mole) freshly prepared dimethylaminopropyl chloride was then added to the solution and the mixture heated on a steam bath for 8 hours. After cooling, the resultant mixture was filtered, and the filtrate concentrated and poured into excess water. The crude base obtained was isolated by ether extraction, followed by back extraction with dilute hydrochloric acid (ca. 2.5*N*), basification, re-extraction with ether and finally removal of the solvent. The crude hydrochloride, obtained by treating an acetone solution of this product with ethereal hydrogen chloride, was recrystallised from iso-propanol and after drying at 110° C yielded 5 - (3′ - dimethylaminopropyl) - 3 - chlorophenanthridone hydrochloride hydrate m.p. 223—226° C. Analysis gave the following results:—

		C(%)	H(%)	N(%)	Cl(%)
	Found	56.9	6.18	7.69	19.1
$C_{18}H_{19}ClN_2O.HCl.1\frac{1}{2}H_2O$	Requires	57.15	6.13	7.4	18.75

EXAMPLE 7

5 - (3′ - Dimethylaminopropyl) - 2 - nitrophenanthridone

To sodium hydride (4.5 g. of a 50% dispersion in oil; ca. 0.94 mole) suspended in dry dimethylformamide (150 ml.) and dry benzene (30 ml.) was added with stirring 2 - nitrophenanthridone (22.4 g; 0.93 mole) and the mixture heated on the steam bath for about ½ hour. To this solution, freshly prepared dimethylaminopropyl chloride (15 g; ca. 0.12 mole) was added and the mixture heated at around 80° C. for 2 hours. The product was filtered cold, and the filtrate concentrated and poured into excess water. The crude base was isolated by extraction with methylene chloride and finally granulation under light petroleum (b.p. 40—60° C.). Crystallisation from acetone and light petroleum (b.p. 40—60° C) gave the pure base, m.p. 113—114° C. Analysis of this product gave the following results:—

		C(%)	H(%)	N(%)
	Found	66.2	6.10	12.9
$C_{18}H_{19}N_3O_3$	Requires	66.5	5.85	12.9

EXAMPLE 8

5 - (3′ - Dimethylaminopropyl) - 2 - nitrophenanthridone hydrochloride monohydrate

An acetone solution of the base from Example 7 was treated with ethereal hydrogen chloride. The crude hydrochloride obtained was recrystallised from ethanol to yield 5 - (3′ - dimethylaminopropyl) - 2 - nitrophenanthridone hydrochloride monohydrate which, after equilibration under normal atmospheric conditions, had a m.p. of 284—286° C. Analysis of this product gave the following results:—

		C(%)	H(%)	N(%)	Cl(%)
	Found	56.5	5.80	11.2	9.41
$C_{18}H_{19}N_3O_3.HCl.H_2O$	Requires	56.9	5.80	11.1	9.35

Such methods of manufacture as have been described in Examples 1 to 8 can, of course, be modified by one skilled in the art to produce any of the novel compounds encompassed by Formula I.

In the following Examples, the active compound 5 - (3′ - dimethylaminopropyl)phenanthridone hydrochloride has been exemplified. This compound may, of course, be replaced wholly or partly in these Examples by any other active compound of the present invention.

EXAMPLE 9

Tablets each having the following composition were made up as described below:

5 - (3′ - Dimethylaminopropyl) - phenanthridone hydrochloride	10 mg
Lactose	48.15 mg.
Maize Starch, dried	41.5 mg.
Sodium lauryl sulphate	0.05 mg.
Magnesium stearate	0.3 mg.

A starch paste, containing 4.5 mg. maize starch in 45 ml. water, was prepared.

The 5 - (3' - dimethylaminopropyl) - phenanthridone hydrochloride, maize starch (29 mg.) sodium lauryl sulphate and lactose were passed through a B.S. No. 44 sieve and mixed well together. The mixed powders were massed with the starch paste and the mass then granulated through a B.S. No. 12 mesh sieve. The granules were dried at 40° C and passed through a B.S. No. 16 mesh sieve. The remainder of the maize starch and the magnesium stearate was passed through a B.S. No. 60 mesh sieve, mixed with the dried granules and the resultant mixture finally compressed to give tablets each weighing 100 mg.

EXAMPLE 10

Tablets each having the following composition were made up as described below:

5 - (3' - Dimethylaminopropyl) - phenanthridone hydrochloride	25 mg.
Lactose	91.3 mg.
Maize Starch, dried	83 mg.
Sodium lauryl sulphate	0.1 mg.
Magnesium stearate	0.6 mg.

A starch paste, containing 9 mg. maize starch in 90 ml. water, was prepared.

The 5 - (3' - dimethylaminopropyl) - phenanthridone hydrochloride, maize starch (58 mg), sodium lauryl sulphate and lactose were passed through a B.S. No. 44 mesh sieve and mixed well together. The mixed powders were massed with the starch paste and the mass granulated through a B.S. No. 12 mesh sieve. The granules were dried at 40° C, passed through a B.S. No. 16 mesh sieve and mixed with the remainder of the maize starch and the magnesium stearate, both the maize starch and magnesium stearate having been previously passed through a B.S. No. 60 mesh sieve. The resultant mixture was finally compressed to give tablets each weighing 200 mg.

EXAMPLE 11

Tablets each having the following composition were made up as described below:—

5 - (3' - dimethylaminopropyl) - phenanthridone hydrochloride	50 mg.
Lactose	123.8 mg.
Maize Starch, dried	125 mg.
Sodium Lauryl sulphate	0.2 mg.
Magnesium stearate	1 mg.

A starch paste, containing 14 mg. maize starch and 140 ml. water, was prepared.

The 5 - (3' - dimethylaminopropyl) - phenanthridone hydrochloride, maize starch (87 mg.), sodium lauryl sulphate, and lactose were passed through a B.S. No. 44 mesh sieve and mixed well together. The mixed powders were massed with the starch paste and the mass granulated through a B.S. No. 12 mesh sieve. The granules were dried at 40° C. passed through a B.S. No. 16 mesh sieve and mixed with the remainder of the maize starch and the magnesium stearate (both passed through a B.S. No. 60 mesh sieve). The resultant mixture was finally compressed to give tablets each weighing 300 mg.

EXAMPLE 12

Capsules each having the following composition were made up as described below:

5 - (3' - dimethylaminopropyl) - phenanthridone hydrochloride	5 mg.
Lactose	145 mg.

The 5 - (3' - dimethylaminopropyl) - phenanthridone hydrochloride and lactose were passed through a B.S. No. 44 mesh sieve, mixed well together and filled into gelatin capsules so that each contained 150 mg. of the mixed powder.

EXAMPLE 13

Capsules each having the following composition were made up as described below:

5 - (3' - dimethylaminopropyl)-phenanthridone hydrochloride	25 mg.
Lactose	175 mg.

The 5 - (3' - dimethylaminopropyl) - phenanthridone hydrochloride and lactose were passed through a B.S. No. 44 mesh sieve, mixed well together and filed into gelatin capsules so that each contained 200 mg. of the mixed powder.

EXAMPLE 14

An elixir having the following composition was made up as described below:

5 - (3' - dimethylaminopropyl) - phenanthridone hydrochloride	100 mg.
Sodium saccharin	120 mg.
Sodium benzoate	100 mg.
Liquid Invert sugar	30.0 ml.
Glycerin	10.0 ml.
Colouring	q.s.
Flavouring	q.s.
Distilled water	100 ml.

The 5 - (3' - dimethylaminopropyl) - phenanthridone hydrochloride, colouring, sodium saccharin and sodium benzoate were dissolved in 30 ml. distilled water. The solution was then diluted with the glycerin and the liquid invert sugar, and finally flavouring added, before making up to a final volume of 100 mls. with distilled water.

Each 5 ml. of elixir contained 5 mg. of 5 - (3' - dimethylaminopropyl) - phenanthridone hydrochloride.

EXAMPLE 15

An elixir having the following composition was made up as described below:

5 - (3′ - dimethylaminopropyl) - phenanthridone hydrochloride	500 mg.
Sodium saccharin	120 mg.
Sodium benzoate	100 mg.
Liquid Invert Sugar	30.0 ml.
Glycerin	10.0 ml.
Colouring	q.s.
Flavouring	q.s.
Distilled water to	100 ml.

The 5 - (3′ - dimethylaminopropyl) - phenanthridone hydrochloride, colouring, sodium saccharin and sodium benzoate were dissolved in 30 ml. of distilled water. The solution was then diluted with the glycerin and the liquid invert sugar, flavouring was added and the elixir made up to a volume of 100 ml. with distilled water.

Each 5 ml. of elixir contained 25 mg. of 5 - (3′ - dimethylaminopropyl) - phenanthridone hydrochloride.

EXAMPLE 16

Suppositories each having the following composition were made up as follows:

5 - (3′ - dimethylaminopropyl-phenanthridone hydrochloride	5 mg.
Oil of Theobroma	1 g.

The 5 - (3′ - dimethylaminopropyl) - phenanthridone hydrochloride was passed through a B.S. No. 85 sieve and triturated with the molten oil of theobroma at 45° C to form a homogeneous suspension. The mixture was stirred well and poured into moulds each of nominal 1 g. capacity to produce suppositories.

EXAMPLE 17

Suppositories each having the following composition were made up as follows:

5 - (3′ - dimethylaminopropyl)-phenanthridone hydrochloride	25 mg.
Oil of Theobroma	1 g.

The 5 - (3′ - dimethylaminopropyl) - phenanthridone hydrochloride was passed through a B.S. No. 85 sieve and triturated with the molten oil of theobroma at 45° C to form a homogeneous suspension. The mixture was stirred well and poured into moulds each of nominal 1 g. capacity to produce suppositories.

EXAMPLE 18

An injection solution having the following composition was made up as described below:

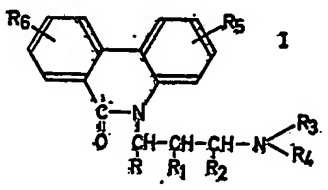
5 - (3′ - dimethylaminopropyl)-phenanthridone hydrochloride	25 mg.
Water for Injection to	2 ml.

The 5 - (3′ - dimethylaminopropyl) - phenanthridone hydrochloride was dissolved in water for injection so that the resultant solution contained 25 mg/2 ml. The solution was filtered through a No. 4 sintered glass filter and distributed into ampoules which were then sealed by fusion of the glass.

These ampoules were sterilised by heating at 115—116° C for 30 minutes.

WHAT WE CLAIM IS:—

1. A compound of the formula:—



wherein R, R_1 and R_2 each represent a hydrogen atom or a methyl radical; R_3 and R_4 each represent a hydrogen atom, or a lower alkyl, cycloalkyl or aralkyl radical, or together with the adjacent nitrogen atom form a heterocyclic ring optionally containing a further hetero atom which hetero atom, when a nitrogen atom, may be substituted by a lower alkyl or hydroxyalkyl radical; and R_5 and R_6 each represent a hydrogen or halogen atom or a lower alkyl, alkoxy, alkylthio, trifluoromethyl, nitro, amino, hydroxyl, cyano or sulphamoyl radical; and acid addition salts thereof.

2. A compound as claimed in claim 1 wherein R_3 and R_4 each represent a hydrogen atom, a lower alkyl or aralkyl radical or together with the nitrogen atom form a heterocyclic ring optionally containing an oxygen atom or a further nitrogen atom, which may be substituted by a lower alkyl or hydroxyalkyl radical, which ring comprises 5 to 7 ring atoms; and R_6 is a hydrogen or halogen atom or a lower alkyl or trifluoromethyl radical; and acid addition salts thereof.

3. A compound as claimed in Claim 2, wherein R, R_1, R_2 and R_6 each represent hydrogen atoms; and R_5 represents a hydrogen or halogen atom or a lower alkyl, nitro, amino or hydroxyl radical; and acid addition salts thereof.

4. 5 - (3′ - Dimethylaminopropyl) - phenanthridone and acid addition salts thereof.

5. 5 - (3′ - Dimethylaminopropyl) - phenanthridone hydrochloride.

6. 5 - (3′ - N - Benzyl - N - methylaminopropyl) - phenanthridone and acid addition salts thereof.

7. 5 - (3′ - N - Benzyl - N - methylaminopropyl) - phenanthridone hydrochloride.

8. 5 - (3′ - Methylaminopropyl) - phenanthridone and acid addition salts thereof.

9. 5 - (3′ - Methylaminopropyl) - phenanthridone hydrochloride.

10. 5 - [3′ - (4″ - Methyl - 1″ - piperazinyl)propyl] - phenanthridone and acid addition salts thereof.

11. 5 - [3′ - 4″ - Methyl - 1″ - piperazinyl)propyl] - phenanthridone dimaleate.

12. 5 - (3' - Dimethylaminopropyl) - 3 - chlorophenanthridone and acid addition salts thereof.

13. 5 - (3' - Dimethylaminopropyl) - 3 - chlorophenanthridone hydrochloride.

14. 5 - (3' - Dimethylaminopropyl) - 2 - nitro - phenanthridone and acid addition salts thereof.

15. 5 - (3' - Dimethylaminopropyl) - 2 - nitrophenanthridone hydrochloride.

16. Pharmaceutical compositions comprising as an essential ingredient at least one active compound or a pharmaceutically acceptable acid addition salt thereof as defined in Claim 1 in association with at least one pharmaceutically acceptable carrier therefor.

17. Compositions as claimed in Claim 16, comprising as an essential ingredient at least one active compound or a pharmaceutically acceptable acid addition salt thereof as defined in Claim 2.

18. Compositions as claimed in Claim 17, comprising as an essential ingredient at least one active compound or a pharmaceutically acceptable acid addition salt thereof as defined in Claim 3.

19. Compositions as claimed in Claim 18 comprising as an essential ingredient at least one active compound or a pharmaceutically acceptable acid addition salt thereof as defined in any one of claims 4 to 15.

20. Compositions as claimed in any one of claims 16 to 19, adapted for oral, rectal or parenteral administration.

21. Compositions as claimed in Claim 20, in the form of tablets, capsules, suppositories suspensions or solutions.

22. Compositions as claimed in Claim 20 and 21, in dosage unit form.

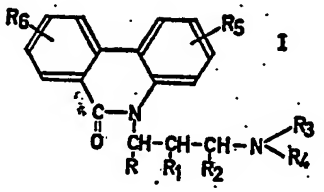
23. Compositions as claimed in claim 22, wherein each dosage unit contains from 0.5 to 500 mg. of the active ingredient.

24. Compositions as claimed in Claim 23, wherein each dosage unit contains from 2 to 110 mg. of the active ingredient.

25. Compositions as claimed in Claim 24, wherein each dosage unit contains from 4 to 80 mg. of the active ingredient.

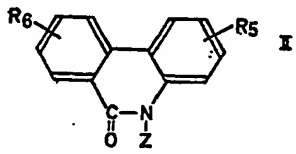
26. Pharmaceutical compositions substantially as described in any one of Examples 9 to 18.

27. Process for preparing a compound of the formula:—



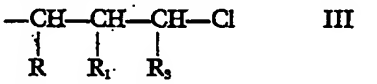
I

or an acid addition salt thereof, wherein R_1 and R_2 each represent a hydrogen atom or methyl radical; R_3 and R_4 each represent a hydrogen atom, or a lower alkyl, cycloalkyl or aralkyl radical, or together with the adjacent nitrogen atom form a heterocyclic ring optionally containing a further hetero atom which hetero atom, when a nitrogen atom, may be substituted by a lower alkyl or hydroxyalkyl radical; and R_5 and R_6 each represent a hydrogen or halogen atom or a lower alkyl, alkoxy, alkylthio, trifluoromethyl, nitro, amino, hydroxyl, cyano or sulphamoyl radical; which method comprises reacting a phenanthridone of the formula:—



I

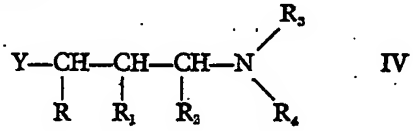
wherein R_5 and R_6 are as defined above and Z is hydrogen or a group of the formula:—



III

wherein R, R_1 and R_2 are as defined above with

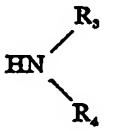
(a) when Z is hydrogen, a compound of the formula:—



IV

wherein R, R_1, R_2, R_3 and R_4 are as defined above and Y is a Cl, Br or I atom or an alkyl- or aryl-sulphonyloxy radical, the reaction being carried out in the presence of a condensing agent; and

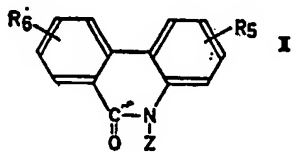
(b) when Z is a group of formula III, an amine of the formula:—



V

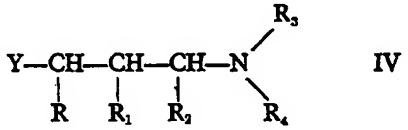
wherein R_3 and R_4 are as defined above; and thereafter, when a compound of formula I in which R_3 and/or R_4 is a hydrogen atom is required and is not obtained by the foregoing method, reducing the corresponding compound of formula I in which R_3 and/or R_4 is an arylmethyl radical; the resultant compounds of formula I being isolated either *per se* or as an acid addition salt thereof.

28. Process as claimed in Claim 27, wherein a compound of the formula:—



I

wherein R_6 and Z are both hydrogen and R_5 is a hydrogen or halogen atom or a lower alkyl, nitro, amino or hydroxyl radical, is reacted with a compound of the formula:—



IV

wherein Y is a Cl, Br or I atom or an alkyl- or aryl-sulphonyloxy radical, each of R, R_1 and R_2 is hydrogen, and R_3 and R_4 each represent a hydrogen atom, a lower alkyl or aralkyl radical or together with the nitrogen atom form a heterocyclic ring optionally containing an oxygen atom or a further nitrogen atom, which may be substituted by a lower alkyl or hydroxyalkyl radical, which ring comprises 5 to 7 ring atoms, the reaction being carried out in the presence of a condensing agent; and thereafter where a compound of formula I, as set forth in Claim 27, in which R_3 and/or R_4 is a hydrogen atom is required and is not obtained by the foregoing method, reducing the correspond compound of formula I in which R_3 and/or R_4 is a benzyl or 2-furfuryl radical using hydrogen in the presence of a hydrogenation catalyst; the resultant compounds of formula I being isolated either *per se* or as an acid addition salt thereof.

29. Process as claimed in Claim 28, wherein R_5 is a hydrogen or halogen atom or a nitro radical and R_3 and R_4 each represent a hydrogen atom, a lower alkyl or benzyl radical or together with the nitrogen atom form a heterocyclic ring, optionally containing a further nitrogen atom which may be substituted by a lower alkyl radical, said ring having 6 ring atoms.

30. Process for preparing phenanthridone derivatives according to Claim 1, substantially as described in any one of Examples 1 to 8.

31. Phenanthridone derivatives, whenever prepared by a process according to any one of Claims 27 to 30.

32. A method of treatment of an animal other than man suffering depression comprising administering to said animal a dose effective for alleviating depression of a compound of the formula set forth in Claim 1, wherein R, R_1 and R_2 each represent a hydrogen atom or a methyl radical; R_3 and R_4 each represent a hydrogen atom, or a lower alkyl, cycloalkyl or aralkyl radical, or together with the adjacent nitrogen atom form a heterocyclic ring optionally containing a further hetero atom which hetero atom, when a nitrogen atom, may be substituted by a lower alkyl or hydroxyalkyl radical; and R_5 and R_6 each represent a hydrogen or halogen atom or a lower alkyl, alkoxy, alkylthio, trifluoromethyl, nitro, amino, hydroxyl, cyano or sulphamoyl radical; or a pharmaceutically acceptable acid addition salt thereof.

NICHOLAS J. FLOWER,
Chartered Patent Agent,
225 Bath Road, Slough, Buckinghamshire,
Agent for the Applicants.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1968.
Published by the Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.